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**Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial**

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Abstract:	Structured, maximum 300 words	266
Main text:	Maximum of 4500 words	3183
Tables/Figures:		2 Tables/5 Figures
Appendix	Yes	5 Tables/2 Figures
References	Maximum of 30	31

**Abstract**

**Background:** Limited treatments with distinct mechanism of action are available for patients with platinum-refractory advanced or metastatic urothelial carcinoma. We assessed efficacy and safety of treatment with docetaxel plus ramucirumab, a human IgG1 VEGFR-2 antagonist, or placebo in this patient population.

**Methods:** In this randomised, double-blind, phase 3 trial, patients with advanced or metastatic urothelial carcinoma who progressed during or after platinum-based chemotherapy were enrolled. Prior treatment with one immune checkpoint inhibitor was permitted. Patients were randomised (1:1) to receive docetaxel 75 mg/m<sup>2</sup> with ramucirumab 10 mg/kg or placebo on day 1 of repeating 21-day cycles until disease progression or other discontinuation criteria were met. The primary endpoint was investigator-assessed progression-free survival. This study is registered with ClinicalTrials.gov, number NCT02426125.

**Findings:** Between July 2015 and April 2017, a total of 530 patients from 124 sites in 23 countries were randomised to receive ramucirumab plus docetaxel (n=263) or placebo plus docetaxel (n=267). Progression-free survival was significantly prolonged in patients treated with ramucirumab plus docetaxel versus placebo plus docetaxel (median, 4·07 vs 2·76 months; HR, 0·757; 95% CI, 0·607-0·943; P=0·0118). A blinded central analysis demonstrated consistent progression-free survival results (HR, 0·672; 95% CI, 0·536-0·842; P=0·0005). Objective response rate was 24·5% (95% CI, 18·8-30·3) in the ramucirumab arm and 14·0% (95% CI, 9·4-18·6) in the placebo arm. Grade ≥3 adverse events were reported at a similar frequency in both arms (60 vs 62%) with no unexpected toxicities.

**Interpretation:** Ramucirumab plus docetaxel is the first regimen in a phase 3 study to show superior progression-free survival over chemotherapy in patients with platinum-refractory advanced urothelial carcinoma.

**Funding:** Eli Lilly and Company

## Introduction

Platinum-based combination chemotherapy is standard frontline treatment for patients with advanced or metastatic urothelial carcinoma (UC) with a median overall survival (OS) of 11–15 months, depending on the type of platinum chemotherapy that can be administered and baseline clinical prognostic factors.<sup>1-4</sup> Despite an objective response rate (ORR) of 40–70%, the duration of response is limited and most patients become refractory. Prognosis in refractory patients remains poor, with a median OS with single-agent cytotoxic therapy of approximately 7 months.<sup>5</sup>

Immune checkpoint inhibitors targeting the programmed death 1 (PD-1) and its ligand (PD-L1) have shown clinical activity in patients with platinum-refractory UC. Accelerated or full approval has been granted in the United States to five agents of this class based on an ORR of 15-21%.<sup>6-10</sup> However, many patients treated with immune checkpoint inhibitors have progressive disease as best response, highlighting other targets and treatments are needed.<sup>6-11</sup>

Vascular endothelial growth factor receptors (VEGFR) 1 and 2 and their ligands are important mediators of tumour angiogenesis and contribute to the pathogenesis and progression of UC.<sup>11-19</sup> Ramucirumab is an immunoglobulin G1 monoclonal antibody that binds to the extracellular domain of VEGFR-2, competing with VEGF-A, -C, and -D.<sup>20</sup> In a randomised phase 2 study in patients with platinum-refractory advanced or metastatic UC, ramucirumab plus docetaxel significantly improved median progression-free survival (PFS) over docetaxel (5·4 vs 2·8 months; hazard ratio [HR], 0·389; 95% confidence interval [CI], 0·235-0·643;  $P=0·0002$ ).<sup>13</sup> To confirm these results, we conducted a randomised phase 3 trial (RANGE) in a similar patient population.

## **Methods**

### **Study design and participants**

We did this double-blind, multicentre randomized, phase 3 study at 124 investigative sites in 23 countries (listed in the appendix). The full inclusion and exclusion criteria are provided in the appendix. Briefly, patients aged 18 years or older were eligible for enrolment if they had histologically or cytologically-confirmed carcinoma of pure or predominant transitional-cell histology; locally advanced or unresectable or metastatic disease extent; primary tumour originating from the bladder, urethra, ureter, or renal pelvis; and progression  $\leq 14$  months after platinum-containing chemotherapy (2 additional months were allowed for screening and patient identification over the standard 12 months<sup>21</sup>). Prior treatment with one immune checkpoint inhibitor was permitted for patients who relapsed  $\leq 24$  months from the end of a platinum-containing regimen, allowing an additional 10 months for patients who received both platinum and immune checkpoint inhibitors. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 was required. Key exclusion criteria included more than one prior systemic chemotherapy in the relapsed or metastatic setting (prior systemic therapy in the perioperative setting was not considered a prior line); prior systemic taxane; untreated brain metastases; haemoglobin  $< 9$  g/dL; and an arterial or venous thromboembolic event  $\leq 6$  months prior to randomisation.

The trial was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable local regulations. The protocol was approved by the ethics committees of all participating centres, and all patients provided written informed consent before study entry. An independent data monitoring committee assessed unblinded safety data throughout the study.

### **Randomisation and masking**

Patients were randomly assigned by a computer-generated random sequence using an interactive Web response system. Randomisation was stratified by geographic region (North America, East Asia, Europe/rest of the world); ECOG performance status at baseline (0 or 1); and visceral metastasis (yes or no), where visceral metastases involve the liver, lung, and/or bone. Patients, study staff, and the sponsor were masked to treatment assignment.

## Procedures

Patients were randomized to receive intravenous (IV) docetaxel 75 mg/m<sup>2</sup> (60 mg/m<sup>2</sup> in Korea, Taiwan and Japan) plus IV ramucirumab 10 mg/kg or placebo 10 mg/kg volume equivalent, on day 1 of a 21-day cycle. Treatments were continued until disease progression or unacceptable toxicity. Docetaxel was limited to 6 cycles; up to 4 additional cycles could be given after sponsor approval. There was no planned crossover on disease progression. Dose modifications of any administered study drug were allowed according to protocol-defined criteria. The use of granulocyte-colony stimulating factors was permitted based on the American Society of Clinical Oncology guidelines.<sup>22</sup>

We assessed tumour response radiographically according to RECIST version 1.1 at baseline, every 6 weeks after randomisation for the first year, and then every 12 weeks thereafter. Following discontinuation, patients were followed for survival every 3 months. The appendix provides details of the timing of other assessments. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for AEs, version 4.0. Patient-reported outcomes (PROs) were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire-Core 30 (QLQ-C30, version 3.0) and the EQ-5D-5L questionnaire, which measure quality of life and health status, respectively. The QLQ-C30 was scored on a scale of 0 to 100, according to the EORTC scoring manual, and the EQ-5D-5L index was calculated using the English value set.<sup>23</sup> For the QLQ-C30, time to sustained deterioration was defined as time from randomisation to first  $\geq 10$ -point worsening with no subsequent on-therapy assessment that returned to or improved from baseline score.

## Outcomes

Primary endpoint was investigator-assessed PFS, defined as the time from randomisation until the first radiographic documentation of objective progression, or as death due to any cause. Secondary endpoints included OS, defined as the time from randomisation to death from any cause; ORR, defined as the proportion of patients with a best overall response of complete or partial response; disease control rate, defined as the proportion of patients with a best overall response of complete response, partial response or stable disease; duration of response, defined as the first date of complete or partial response until the first date of objective progression, or death; safety; PROs;

pharmacokinetics of ramucirumab; and immunogenicity of ramucirumab. The protocol provides the full assessment schedule.

### **Statistical analysis**

We planned to enrol 524 patients in a 1:1 randomisation with the primary analysis to be conducted when at least 331 PFS events were observed from the first 437 randomised patients. The number of events provided 90% power to detect PFS superiority of ramucirumab plus docetaxel versus placebo plus docetaxel, assuming a HR of 0.70 with a 2-sided alpha of 0.05. The sample size was also adequately powered to show an OS superiority between the 2 arms, with an assumed HR of 0.75 for ramucirumab plus docetaxel versus placebo plus docetaxel with at least 382 events, power 80%, and 2-sided type I error of 0.05.

PFS and response were assessed in the first 437 patients of the intention-to-treat (ITT) population that included all randomised patients. PROs used the full ITT population. PFS was estimated using the Kaplan-Meier method, and outcomes were compared between arms using a stratified log-rank test. HRs and associated 95% CIs were estimated using a stratified Cox proportional hazard model. The PRO data were summarised descriptively. Time to sustained deterioration was compared using an unstratified log-rank test. Safety was assessed in all patients who received at least one dose of study medication. A gatekeeping design was implemented to assess PFS, OS, and ORR in a fixed sequential manner.

### **Role of the Funder**

The trial was designed by the funder (Eli Lilly and Company), in collaboration with the scientific council (including authors: DPP, RdW, KNC, CNS, HN, and TP), and was responsible for data management, and statistical analysis. The funder interpreted data in collaboration with all authors and supported development of the report by providing medical writing and editorial assistance. All authors made the decision to submit the report for publication.

## Results

### Patients and Treatment

Between July 2015 and April 2017, a total of 727 patients at 124 sites were screened, and 530 eligible patients were randomly assigned to receive ramucirumab plus docetaxel (n=263) or placebo plus docetaxel (n=267). Five patients in the ramucirumab arm and two in the placebo arm did not receive study treatment; therefore, the safety population comprised 523 patients (Figure 1). Baseline characteristics of the treatment arms were well balanced (Tables 1, S1, S2). Most patients (61%) had two or more adverse prognostic risk factors,<sup>24,25</sup> including visceral metastases (70%), haemoglobin <10 g/dL (14%), ECOG performance status score >0 (53%), and time since completion or discontinuation of previous therapy of <3 months (45%) (Table 1).

Data cutoff for the current analysis was April 21, 2017, at which time 341 of the first 437 randomised patients had disease progression or died. At data cutoff, 49 (19%) of 263 patients in the ramucirumab arm and 36 (13%) of 267 patients in the placebo arm continued to receive study treatment. Median follow-up duration in the full ITT population was 5·0 months (interquartile range [IQR], 2·3–8·9).

Median therapy duration was 12·2 weeks (IQR, 6·0–21·0) with ramucirumab and 9·9 weeks (IQR, 6·0–20·9) with placebo. The median number of cycles of docetaxel was four (IQR, 2–6) in the ramucirumab arm and three (IQR, 2–6) in the placebo arm (Table S3). Ninety-three (36%) of 258 patients in the ramucirumab arm and 84 (32%) of 265 patients in the placebo arm completed at least six cycles of docetaxel therapy; median relative dose intensities were 98·3% (IQR, 90·9–100·1) and 98·8% (IQR, 92·9–100·1), respectively. Patients who continued with ramucirumab or placebo monotherapy after the end of docetaxel (n=64 versus n=60) received a median of three (IQR, 2–7) additional cycles of treatment in the ramucirumab arm and two (IQR, 1–5) in the placebo arm.

### Outcomes

Table S4 summarises the efficacy results. In the 437 ITT population, 341 PFS events occurred (ramucirumab arm: n=158 [73%]; placebo arm: n=183 [83%]). Median PFS was 4·07 months in the ramucirumab arm and 2·76 months in the placebo arm (stratified HR, 0·757; 95% CI, 0·607–0·943; P=0·0118; Figure 2A). The estimated PFS rate at 12 months was 11·9% (95% CI, 7·1–18·0) in the



ramucirumab arm and 4.5% (95% CI, 1.5–10.1) in the placebo arm. A blinded independent central analysis demonstrated consistent PFS results (stratified HR, 0.672; 95% CI, 0.536–0.842;  $P=0.0005$ ; Figure 2B). In prespecified subgroup analyses for PFS, the addition of ramucirumab to docetaxel improved PFS across most patient subgroups (Figure 3).

Investigator-assessed ORR in the 437 ITT population was 24.5% (95% CI, 18.8–30.3) in the ramucirumab arm and 14.0% (95% CI, 9.4–18.6) in the placebo arm, with non-overlapping confidence intervals (Table S4). This included nine (4.2%) complete responses in the ramucirumab arm and three (1.4%) complete responses in the placebo arm. ORR by blinded independent central analysis was 22.2% (95% CI, 16.7–27.8) in the ramucirumab arm and 12.7% (95% CI, 8.3–17.1) in the placebo arm. Due to gatekeeping trial design, ORR superiority will be formally tested if the OS superiority test is positive. Median duration of response was 5.65 months (95% CI, 3.9–7.1) for the ramucirumab arm and 4.17 months (95% CI, 2.9–5.5) for the placebo arm. Of the patients who received a prior immune checkpoint inhibitor, 5 (35.7%) of 14 patients in the ramucirumab arm and 2 (10.5%) of 19 in the placebo arm had an objective response to treatment. Disease control occurred in 63.4% (95% CI, 57.0–69.8) of patients in the ramucirumab arm and 56.1% (95% CI, 49.6–62.7) in the placebo arm. Most patients experienced a reduction in tumour burden, with an observed increase in PFS, in the ramucirumab arm (64%) (Figure 4). Reductions in tumour burden occurred less frequently in the placebo arm (47%). As of the data cutoff, OS results were not mature, with 219 events.

Compliance for completion of the PRO questionnaires in the 530 ITT population was 97% in both treatment arms at baseline and was  $\geq 85\%$  at all on-therapy post-baseline visits. Baseline scores were similar between treatment arms. Mean scores for global quality of life and the EQ-5D-5L index were relatively unchanged over time, with no differences between treatment arms (Figure 5). There was no difference in time to sustained deterioration in global quality of life (unstratified HR, 0.931; 95% CI, 0.701–1.235;  $P=0.610$ ).

Following administration of ramucirumab 10 mg/kg every 3 weeks in combination with docetaxel to patients with urothelial carcinoma, the geometric mean trough concentrations prior to doses 2, 3 and 5 were 15, 23, and 34  $\mu\text{g/mL}$ , respectively. These data are consistent with previous studies where

ramucirumab was administered to patients with various types of cancer using this regimen. Of the 258 treated patients in the ramucirumab arm, there were 185 whose serum was analysed for the presence of anti-ramucirumab antibodies; 19 (10%) had positive samples at baseline and 3 (2%) had treatment-emergent anti-ramucirumab antibodies.

### **Safety**

The most frequently reported treatment-emergent AEs in either treatment arm (any grade) were fatigue, alopecia, diarrhoea, decreased appetite, and nausea (Table 2). These occurred predominantly at grade 1–2 severity. Grade  $\geq 3$  AEs were reported at a similar frequency in both treatment arms; 60% of patients in the ramucirumab arm and 62% in the placebo arm. No grade  $\geq 3$  AE was observed that showed a difference in incidence of 5% or more in the ramucirumab arm compared to placebo. Grade  $\geq 3$  anaemia was less common in the ramucirumab arm (3 vs 11%). The incidence of grade  $\geq 3$  neutropenia (15 vs 14%) was similar in both treatment groups. Granulocyte colony-stimulating factor use was similar in both treatment groups: 41% in the ramucirumab arm and 42% in the placebo arm.

AEs of interest, based on the known safety profile of other antiangiogenic therapies and prior clinical experience with ramucirumab, are shown in Table 2. Grade 1-2 events of epistaxis (14 vs 5%), hypertension (11 vs 5%), haematuria (10 vs 6%), and proteinuria (9 vs 3%) were each reported more frequently in the ramucirumab arm. The incidence of venous (2 vs 5%) and arterial (3 vs <1%) thromboembolic events were low and reported at similar frequency in both treatment groups.

AEs leading to at least one dose adjustment (reduction, delay or omission of any study drug) were reported in 88 (34%) patients in the ramucirumab arm and 82 (31%) in the placebo arm. The most common AE leading to dose adjustments for ramucirumab compared with placebo was febrile neutropenia (4 vs 4%). AEs leading to discontinuation of any study treatment occurred in 39 (15%) patients in the ramucirumab arm and 19 (7%) in the placebo arm. Sepsis was the most common AE leading to treatment discontinuation of any therapy; this occurred in five (2%) patients in ramucirumab arm and no patients in the placebo arm.

Serious AEs were reported for 100 (39%) patients in the ramucirumab arm and 104 (39%) in the placebo arm; these were deemed to be related by the investigator to study treatment in 63 (24%) and 54 (20%), respectively. Including events related by the investigator to disease progression, AEs with an outcome of death on treatment or within 30 days of discontinuation were reported for 38 (15%) patients in the ramucirumab arm and 43 (16%) in the placebo arm; these were deemed to be related by the investigator to study treatment in 8 (3%) and 5 (2%) patients, respectively. Sepsis was the most common AE leading to death on therapy (Table S5), occurring in 4 (2%) patients in ramucirumab arm and no patients in the placebo arm. One fatal event of neutropenic sepsis was reported in the ramucirumab arm.

## Discussion

The RANGE study demonstrated the addition of ramucirumab to docetaxel was associated with a statistically significant improvement in PFS in patients with platinum-refractory advanced UC. In this advanced patient population, PFS outcomes were consistent across almost all major subgroups examined and confirmed by blinded central review. The majority of patients in this trial had two or more adverse prognostic risk factors at baseline, including the presence of visceral metastases. A consistent PFS benefit was observed for patients treated with ramucirumab plus docetaxel, irrespective of these risk factors, demonstrating broad applicability of this regimen. The median PFS of 2.76 months that was observed in the placebo arm is consistent with historical data in the second-line setting, such that the observed improvement in the ramucirumab arm was not attributable to underperformance of the control arm.<sup>5,13</sup>

OS data are immature at this time precluding formal statistical analysis for ORR in accordance with the order of analyses specified in the statistical analysis plan. However, a higher proportion of patients achieved an objective response in the ramucirumab arm (24.5%), including nine complete responses, than in the placebo arm (14.0%) with non-overlapping 95% CIs. The ORR was consistent with that of the phase 2 study of this treatment regimen and higher when indirectly compared with historical chemotherapy studies.<sup>5,13,26</sup> The ORR observed in the ramucirumab arm in our study is also in line with those seen with immune checkpoint inhibitors in other studies, although duration of response appears longer with immune checkpoint inhibitors.<sup>6</sup> The disease control rate of 63.4% in our study

compares favourably to single-agent chemotherapy or immune checkpoint inhibitors in other studies, underlining the active nature of this regimen in biomarker-unselected patients.

The combination of ramucirumab and docetaxel revealed no unexpected safety findings. Most toxicities were of grade 1–2 severity and manageable with supportive care alone or with dose reductions, as evident by the high median relative dose-intensity for all study drugs. Overall, the addition of ramucirumab to docetaxel was not associated with an increase in occurrence of grade  $\geq 3$  toxicities typically associated with docetaxel in this patient population. Consistent with Phase 2 data,<sup>13</sup> the most common haematological toxicity in our study was neutropenia and was reported at a similar incidence in both treatment arms; anaemia was less common in the ramucirumab arm. The incidence of toxicities identified as potential class effects of antiangiogenic therapies, such as grade 1–2 hypertension and bleeding, occurred at a higher frequency in the ramucirumab arm. In addition, the PRO analyses indicated that there was no negative impact on quality of life. This is particularly important for these patients, as most have a short life expectancy.

Phase 2 and 3 studies have demonstrated that approximately 20% of patients with platinum-refractory UC demonstrate an objective response to immune checkpoint inhibition.<sup>6-8</sup> Strategies to increase ORR include combinations of PD-1/PD-L1 inhibitors with other immune checkpoint inhibitors, chemotherapy, or antiangiogenic agents.<sup>5,27-30</sup> Ramucirumab in combination with PD-1/PD-L1 inhibitors has demonstrated promising clinical activity in multiple tumour types in the phase 1 setting, with no unexpected toxicities.<sup>28,30,31</sup> Although the pool of patients in RANGE who had been treated with prior immune checkpoint inhibitors is limited, the reported outcome is similar to that observed in all patients. Based on the reported efficacy and tolerability, ramucirumab plus docetaxel is also an alternative treatment regimen in the post-immune checkpoint or immune checkpoint inhibitor ineligible setting.

In conclusion, these findings are consistent with results from our previous phase 2 study in which ramucirumab combined with docetaxel improved PFS in patients with platinum-refractory advanced or metastatic UC. Ramucirumab is the only antiangiogenic agent with proven clinical activity in this patient population and, to our knowledge, RANGE represents the first phase 3 study to demonstrate a PFS

advantage over chemotherapy alone. No additive or unexpected toxicities were observed when ramucirumab was combined with docetaxel. Together, these studies suggest a favorable benefit-to-risk ratio for this combination treatment and may represent a new regimen for this patient population.

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### **Research in context**

#### **Evidence before this study**

In the development of the study design and protocol, we conducted a systematic review of the published scientific literature. We searched PubMed, with no time restrictions; abstracts of major oncology congresses; and clinical trial websites including ClinicalTrials.gov, for English-language preclinical reports and clinical trials assessing chemotherapy, antiangiogenic therapies, and a combination of these methods in urothelial carcinoma. The findings of this search included multiple single-agent cytotoxic therapies, such as docetaxel, all with modest activity in this patient population. Search results for clinical data in support of this trial included a randomised phase 2 study (NCT01282463) in patients with platinum-refractory advanced or metastatic UC, where ramucirumab plus docetaxel significantly improved median progression-free survival (PFS) over docetaxel. As the protocol was being developed, emerging evidence suggested immune checkpoint inhibitors targeting the programmed death 1 (PD-1) and its ligand (PD-L1) demonstrated clinical activity in a subset of patients with platinum-refractory UC. On the basis of this emerging evidence, we included patients who received one prior immune checkpoint inhibitor. Upon review of the scientific literature and discussions with clinicians, researchers, and regulatory agencies, we conducted this phase 3 study.

**Added value of this study**

Our findings show that in patients with platinum-refractory advanced or metastatic urothelial carcinoma, ramucirumab plus docetaxel can improve PFS and the objective response rate, without additive toxicity or compromising quality of life when compared to placebo plus docetaxel. The response rate observed in our trial is in line with those seen with immune checkpoint inhibitors in other studies. Taken together with results from our prior phase 2 study in a similar patient population, we provide significant data showing inhibition of VEGFR-2-mediated signaling yields meaningful clinical activity in patients with platinum-refractory advanced or metastatic urothelial carcinoma. Ramucirumab is the only antiangiogenic agent with meaningful clinical activity in this patient population and, to our knowledge, RANGE is the first phase 3 study to demonstrate a PFS advantage over chemotherapy alone in platinum-refractory advanced or metastatic urothelial carcinoma.

**Implications of all the available evidence**

The RANGE trial design was appropriate for the treatment of a patient population with platinum-refractory advanced or metastatic urothelial carcinoma and can be generalized to clinical practice. The results confirm the benefit of the addition of an anti-VEGFR2 antibody to standard chemotherapy in this setting and represent clinically meaningful progress in the treatment of urothelial carcinoma.

**Contributors**

DPP, RdW, KNC, CNS, HN, and TP were members of the scientific council and contributed to study design, data collection, data analysis, data interpretation, and drafting, review, and approval of the submitted report. AML, RAW, OH, and AHZ contributed to study design, data analysis, data interpretation, and drafting, review, and approval of the submitted report. RCW and KMB-M contributed to data analysis, data interpretation, and drafting, review, and approval of the submitted report. BA, IJP, FL, and AR-V: contributed to data collection, data analysis, data interpretation, and review and approval of the submitted report. AB, HSC, MH, MT, GT, XGdM, and HH contributed to data collection, and review and approval of the submitted report. DC, SH, EYY and IC contributed to

data analysis, data interpretation, and drafting, review, and approval of the submitted report. AD, AF, MvdH, NM, AN, Y-CO, W-PS, J-LL, AS, and SS contributed to data collection, data interpretation, and drafting, review and approval of the submitted report. LG contributed to data interpretation, and review and approval of the submitted report.

### **Declaration of Interests**

**DPP** reports grants from Eli Lilly and Company, during the conduct of the study; personal fees from Bayer, Bellicum, Dendreon, Sanofi Aventis, Johnson and Johnson, Exelixis, Ferring, Millineum, Medivation, Pfizer, Roche Laboratories, and Tyme pharmaceuticals, grants from Oncogenix, Progenics, Johnson and Johnson, Merck, Millineum, Dendreon, Sanofi Aventis, Agensys, Eli Lilly and Company, and Roche Laboratories; and other from Bellicum and Tyme, outside the submitted work.

**RdW** reports personal fees from Eli Lilly and Company, during the conduct of the study, and personal fees from Merck, Roche, and Sanofi, outside the submitted work. **KNC** reports institutional funding from Eli Lilly and Company, during the conduct of the study. **CNS** reports personal fees from Eli Lilly and Company, BMS, Merck/Pfizer, and Clovis, outside the submitted work. **SH** reports personal fees from Roche, Merck, Astra Zeneca, Pierre Fabre, and Bayer, outside the submitted work. **AF** reports personal fees from Astra Zeneca, MSD, Pierre Fabre, Pfizer, and Roche, outside the submitted work.

**AB** reports personal fees from Astra Zeneca and BMS, and grants and personal fees from Roche, outside the submitted work. **EYY** reports grants and personal fees from Eli Lilly and Company, during the conduct of the study; grants and personal fees from Agensys, Astellas, Bayer, Dendreon, Genentech/Roche, and Merck; and personal fees from AstraZeneca, Churchill Pharmaceuticals, EMD Serono, Ferring, Janssen, Medivation, Sanofi, Seattle Genetics, Tolmar, and Tokai, outside the submitted work. **MSvdH** reports personal fees from Roche/Genentech, AstraZeneca/Medimmune, BMS, grants and personal fees from Astellas, outside the submitted work. **AN** reports grants, personal fees and non-financial support from Roche, grants and personal fees from Merck, and Astra Zeneca; and personal fees from Seattle Genetics, and Bayer, during the conduct of the study. **MT** reports personal fees from Astellas, Sanofi, Bayer, and Janssen, outside the submitted work. **AP** reports other from MSD, Bayer, BMS, Janssen, Astellas, Novartis, Roche, Astra Zeneca, and Pfizer, outside the submitted work. **XGdM** reports personal fees from Pfizer, BMS, Eli Lilly and Company, Pharmamar, Novartis, Ipsen, and Roche, outside the submitted work. **RCW, AML, OH, AHZ,** and

**KMB-M** are employees and shareholders at Eli Lilly and Company. **RAW** is an employee, shareholder, and has a patent pending at Eli Lilly and Company. **TP** reports grants and other from Roche, grants from AZ, and personal fees from Roche, Merck, AZ, BMS, Eli Lilly and Company, and Pfizer, outside the submitted work. **AD, HN, DC, NM, BA, LG, Y-CO, HSC, W-PS, MH, IJP, J-LL, AS, FL, GT, SS, AR-V, IC, and HH** declare no competing interests.



**Table 1. Baseline demographics and characteristics (ITT; n=530)**

	<b>Ramucirumab + docetaxel (n=263)</b>	<b>Placebo + docetaxel (n=267)</b>
Median age, years (range)	65 (34-86)	66 (32-83)
≥ 65 years	139 (53)	152 (57)
Male sex	213 (81)	215 (81)
Race		
White	204 (78)	204 (76)
Asian	54 (21)	61 (23)
ECOG performance status		
0	121 (46)	125 (47)
1	138 (52)	142 (53)
Geographical region		
North America	24 (9)	24 (9)
Europe/Other	186 (71)	186 (70)
East Asia	53 (20)	57 (21)
Histology		
Pure transitional cell	201 (76)	209 (78)
Mixed histology	55 (21)	50 (19)
Missing	7 (3)	8 (3)
Bladder as primary site of tumour	169 (64)	170 (64)
Visceral disease	182 (69)	188 (70)
Lung metastases	99 (38)	121 (45)
Liver metastases	78 (30)	69 (26)
Bone metastases	56 (21)	53 (20)
Adrenal gland	16 (6)	12 (4)
Kidney	12 (5)	10 (4)
Spleen	4 (2)	5 (2)
Other	35 (13)	28 (10)
Lymph node only metastases	52 (20)	45 (17)
Creatinine clearance		
<60 mL/min	106 (40)	118 (44)
≥60 mL/min	151 (57)	146 (55)
Missing	6 (2)	3 (1)

Haemoglobin concentration <10 g/dL	37 (14)	36 (13)
Completion or disc of most recent therapy < 3 months	115 (44)	122 (46)
Number of Bellmunt risk factors <sup>†</sup>		
0	3 (1)	0
1	102 (39)	101 (38)
2	88 (33)	113 (42)
3	69 (26)	45 (17)
4	1 (<1)	8 (3)
Prior adjuvant therapy		
Adjuvant	38 (14)	61 (23)
Neo-adjuvant	40 (15)	37 (14)
No prior adjuvant	168 (64)	155 (58)
Missing	17 (6)	14 (5)
Prior therapies <sup>‡</sup>		
Cisplatin-based	159 (60)	182 (68)
Carboplatin-based	95 (36)	78 (29)
Immune checkpoint inhibitor	18 (7)	26 (10)

Abbreviation: disc = discontinuation; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat.

Data are n (%) unless otherwise indicated.

<sup>†</sup>Bellmunt risk factors<sup>24,25</sup> included visceral metastases, hemoglobin <10 g/dL, ECOG performance status score >0, and time since completion or discontinuation of previous therapy of <3 months.

<sup>‡</sup>A detailed summary of prior anticancer therapies is included in Table S2.

**Table 2: Treatment-emergent adverse events (safety population, n=523)**

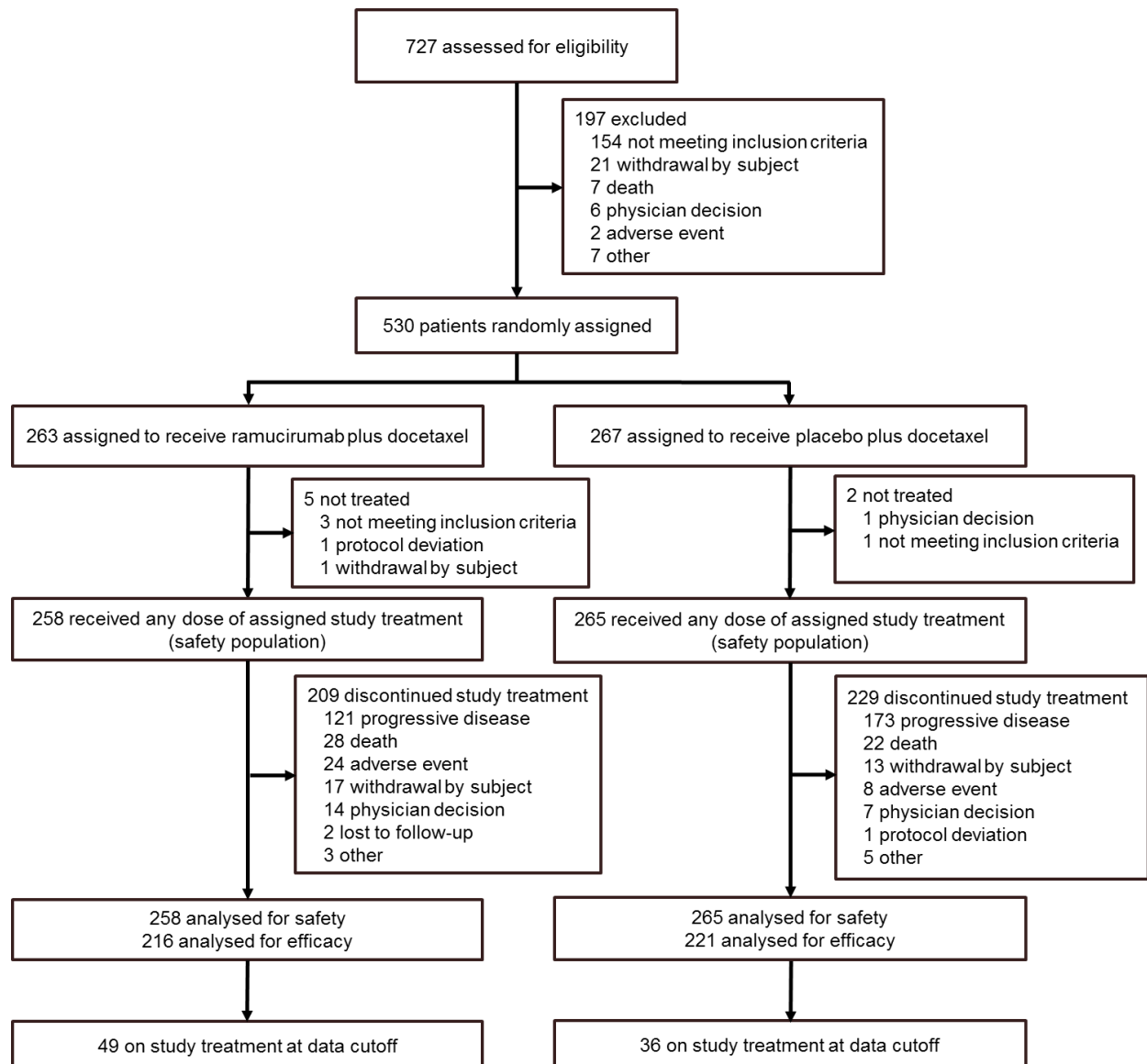
	<b>Ramucirumab + docetaxel (n=258)</b>		<b>Placebo + docetaxel (n=265)</b>	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
<b>Any</b>	244 (95)	156 (60)	251 (95)	163 (62)
Fatigue <sup>†</sup>	110 (43)	20 (8)	121 (46)	25 (9)
Alopecia	63 (24)	0	92 (35)	1 (<1)
Diarrhoea	75 (29)	7 (3)	56 (21)	7 (3)
Decrease appetite	73 (28)	8 (3)	61 (23)	5 (2)
Nausea	63 (24)	1 (<1)	52 (20)	3 (1)
Stomatitis	61 (24)	8 (3)	29 (11)	0
Pyrexia	42 (16)	1 (<1)	41 (15)	1 (<1)
Vomiting	38 (15)	3 (1)	37 (14)	2 (<1)
Neuropathy <sup>†</sup>	31 (12)	0	43 (16)	2 (<1)
Constipation	29 (11)	1 (<1)	43 (16)	1 (<1)
Urinary tract infection	32 (12)	10 (4)	38 (14)	11 (4)
Peripheral oedema	36 (14)	0	30 (11)	1 (<1)
Dyspnoea	30 (12)	5 (2)	30 (11)	5 (2)
Asthenia	26 (10)	3 (1)	22 (8)	4 (2)
Dysgeusia	30 (12)	0	17 (6)	0
<b>Haematological</b>				
Neutropenia <sup>†</sup>	51 (20)	39 (15)	44 (17)	36 (14)
Febrile neutropenia	25 (10)	25 (10)	17 (6)	17 (6)
Anaemia	40 (16)	7 (3)	64 (24)	28 (11)
Leukopenia <sup>†</sup>	26 (10)	17 (7)	24 (9)	21 (8)
<b>AEs of special interest</b>				
Bleeding or haemorrhage <sup>†</sup>	67 (26)	8 (3)	46 (17)	12 (5)
Epistaxis	36 (14)	0	13 (5)	0
Haematuria	27 (10)	5 (2)	17 (6)	5 (2)
GI haemorrhage	10 (4)	2 (<1)	10 (4)	3 (1)
Pulmonary haemorrhage	1 (<1)	0	0	0
Hypertension <sup>†</sup>	29 (11)	15 (6)	12 (5)	5 (2)
Renal failure <sup>†</sup>	15 (6)	8 (3)	19 (7)	2 (<1)
Proteinuria	23 (9)	2 (<1)	8 (3)	1 (<1)
Venous thromboembolic <sup>†</sup>	6 (2)	1 (<1)	13 (5)	5 (2)
Arterial thromboembolic <sup>†</sup>	8 (3)	6 (2)	2 (<1)	0

Fistula <sup>†</sup>	5 (2)	3 (1)	2 (<1)	2 (<1)
Congestive heart failure <sup>†</sup>	3 (1)	2 (<1)	1 (<1)	1 (<1)
GI perforation <sup>†</sup>	3 (1)	2 (<1)	1 (<1)	1 (<1)

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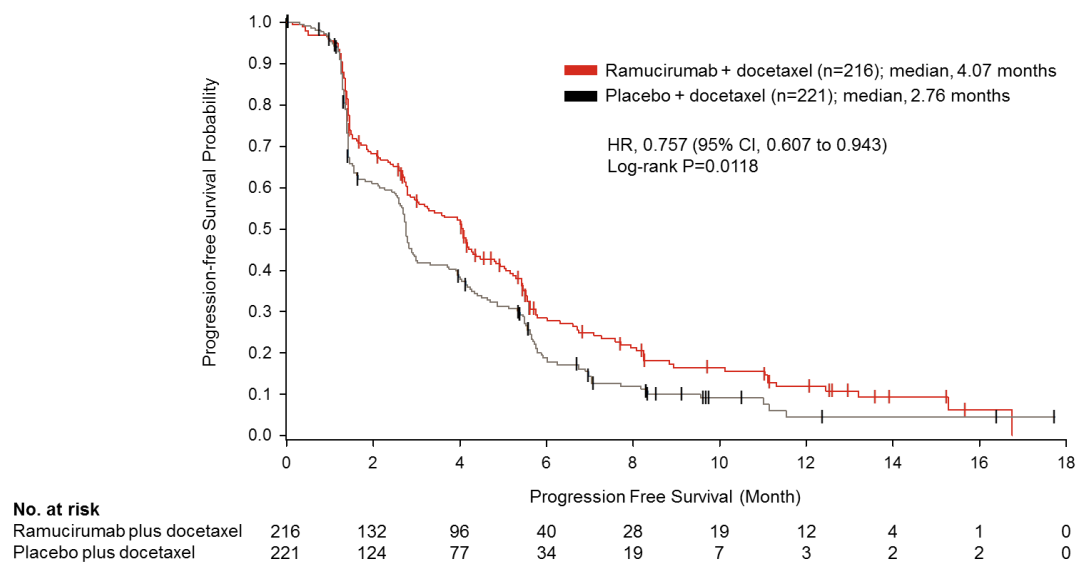
Abbreviation: AE = adverse event; GI = gastrointestinal.

Data are number (%). The table shows treatment-emergent adverse events occurring in at least 10% of patients or of special interest irrespective of cause, according to either preferred terms or <sup>†</sup>consolidated categories.

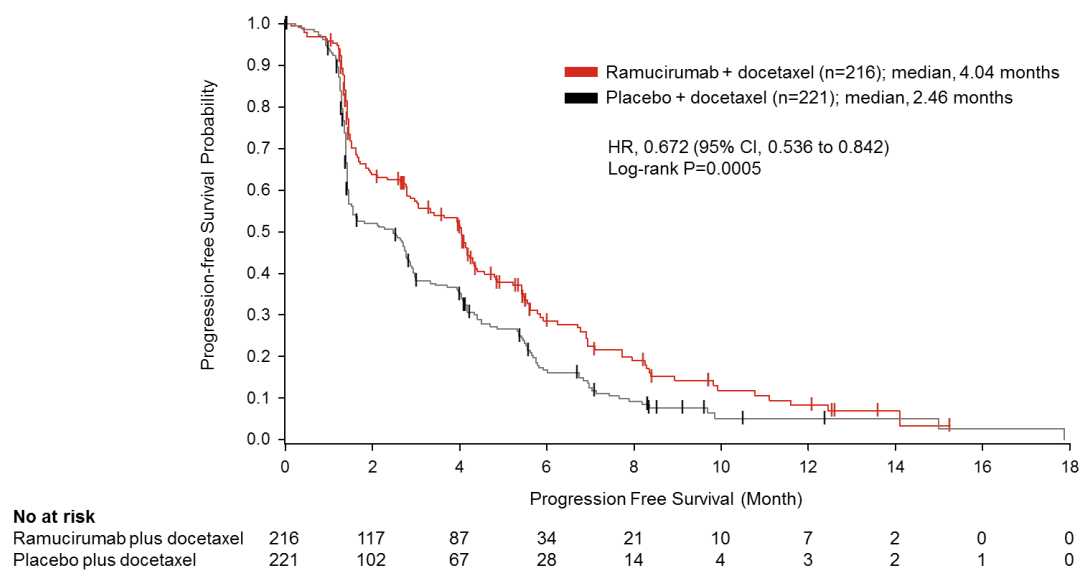
**Figure 1: Trial Profile**

**Figure 2: Kaplan-Meier plots for progression-free survival (n=437). (A) investigator-assessed (B) independent central review. Abbreviations: CI = confidence interval; HR = hazard**

A

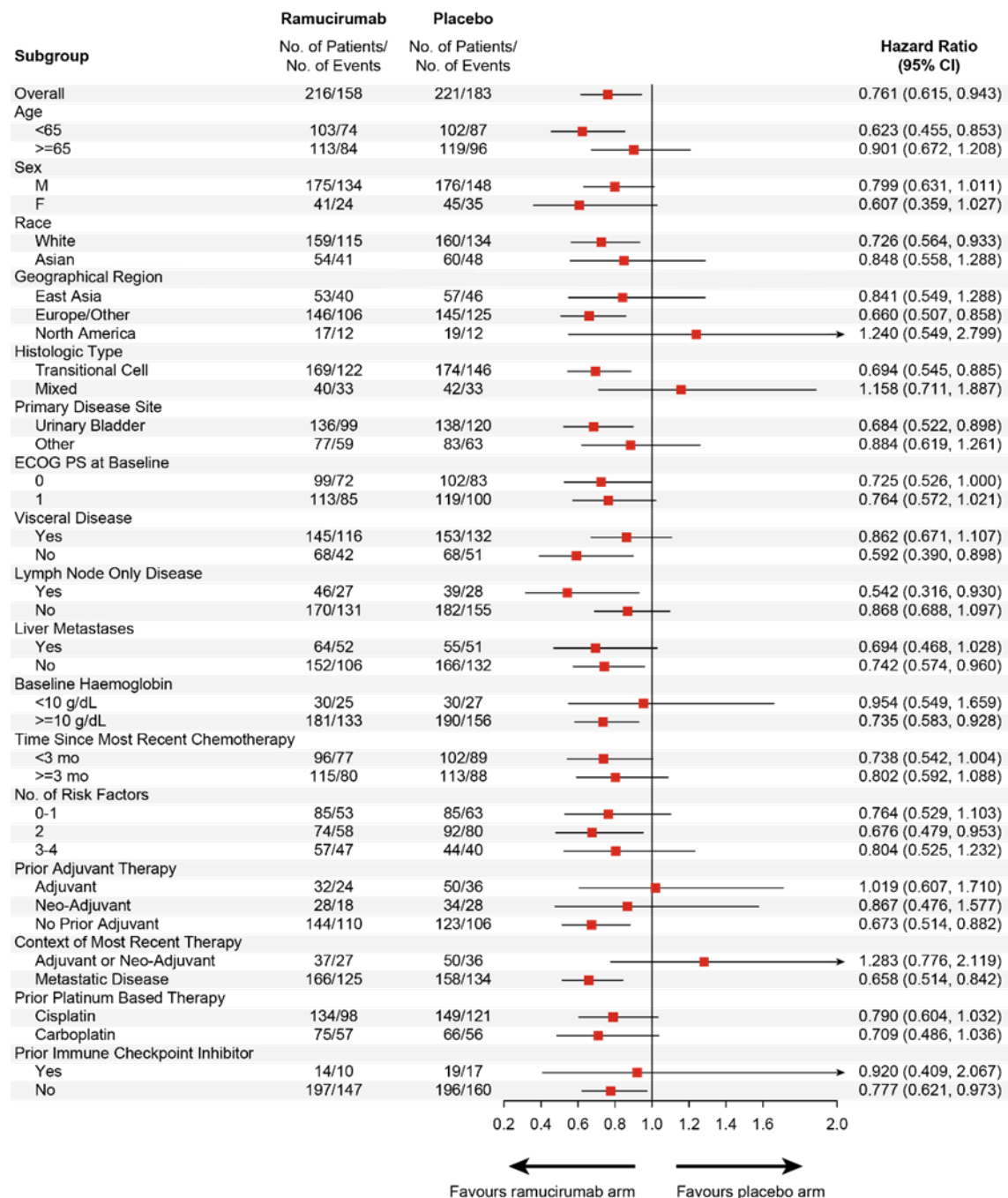


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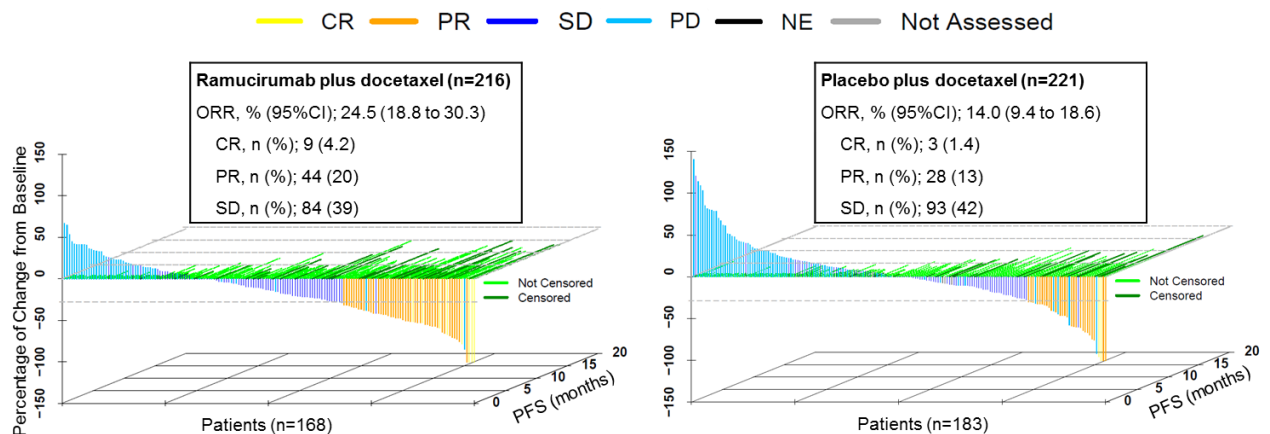


**Figure 3: Progression-free survival subgroup analyses, first 437 randomised patients**

**Abbreviations:** CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; F = female; M = male.



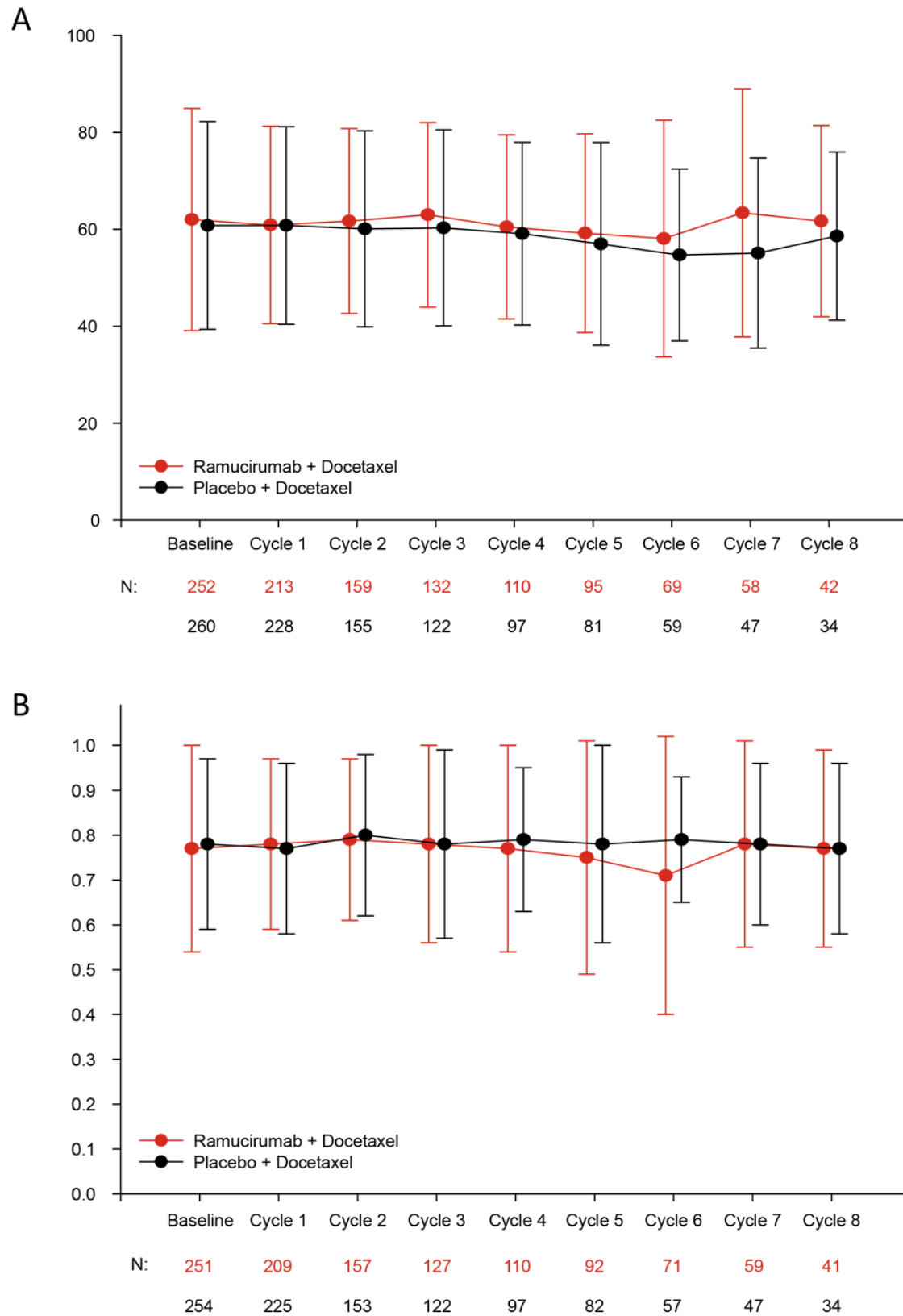
**Figure 4: Best percent change from baseline in tumour size vs progression-free survival (PFS), first 437 randomised patients**



Best percentage change of targeted lesions from baseline versus PFS. Patients (x-axis) were ordered by best percentage change of targeted lesions from baseline (y-axis) and color coded for best response according to RECIST version 1.1. PFS time (z-axis) is shown as observed or censored at time of data cutoff. Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease; ORR = objective response rate. ORR was determined in the first 437 ITT population.



**Figure 5: Patient-reported Outcome Scores by Visit: (A) EORTC QLQ-C30 Global Quality of Life and (B) EQ-5D-5L index**



Circles represent means scores and bars represent standard deviation. (A) Scores range from 0 to 100, with higher scores representing better quality of life. (B) Scores range from -0.281 to 1 (displayed as 0-1), with higher scores representing better health status. These figures offset data from the treatment arms along the x-axis for increased legibility, but the assessment times were the same for both arms.

**APPENDIX****Study Protocol (attached separately)****List of Principal Investigators**

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**Table S1: Baseline demographics, first 437 randomised patients**

	<b>Ramucirumab + docetaxel (n=216)</b>	<b>Placebo + docetaxel (n=221)</b>
Median age, years (range)	65 (34-86)	66 (34-83)
≥ 65 years	113 (53)	119 (54)
Male sex	175 (81)	176 (80)
Race		
White	159 (74)	160 (72)
Asian	54 (25)	60 (27)
ECOG performance status		
0	99 (46)	102 (46)
1	113 (52)	119 (54)
Geographical region		
North America	17 (8)	19 (9)
Europe/Other	146 (68)	145 (66)
East Asia	53 (25)	57 (26)
Histology		
Pure transitional cell	169 (78)	174 (79)
Mixed histology	40 (19)	42 (19)
Missing	7 (3)	5 (2)
Primary site of tumour		
Bladder	136 (63)	138 (62)
Renal pelvis	30 (14)	35 (16)
Ureter	32 (15)	29 (13)
Urethra	5 (2)	5 (2)
Other	10 (5)	14 (6)
Missing	3 (1)	0
Visceral disease	145 (67)	153 (69)
Lung metastases	78 (36)	102 (46)
Liver metastases	64 (30)	55 (25)
Bone metastases	47 (22)	46 (21)
Adrenal gland	13 (6)	8 (4)
Kidney	7 (3)	7 (3)
Spleen	3 (1)	3 (1)
Other	30 (14)	20 (9)
Lymph node only metastases	46 (21)	39 (18)

Creatinine clearance		
<60 mL/min	92 (43)	101 (46)
≥60 mL/min	119 (55)	118 (53)
Missing	5 (2)	2 (<1)
Haemoglobin concentration <10 g/dL	30 (14)	30 (14)
Completion or disc of most recent therapy < 3 months	96 (44)	102 (46)
Number of Bellmunt risk factors <sup>†</sup>		
0	3 (1)	0
1	82 (38)	85 (38)
2	74 (34)	92 (42)
3	56 (26)	37 (17)
4	1 (<1)	7 (3)
Prior adjuvant therapy		
Adjuvant	32 (15)	50 (23)
Neo-adjuvant	28 (13)	34 (15)
No prior adjuvant	144 (67)	123 (56)
Prior therapies <sup>‡</sup>		
Cisplatin-based	134 (62)	149 (67)
Carboplatin-based	75 (35)	66 (30)
Immune checkpoint inhibitor	14 (6)	19 (9)

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Abbreviation: disc = discontinuation; ECOG = Eastern Cooperative Oncology Group.

Data are n (%) unless otherwise indicated.

<sup>†</sup>Bellmunt risk factors<sup>24,25</sup> included visceral metastases, haemoglobin <10 g/dL, ECOG performance status score >0, and time since completion or discontinuation of previous therapy of <3 months.

<sup>‡</sup>A detailed summary of prior anticancer therapies is included in Table S2.

**Table S2: Prior therapies<sup>†</sup> (ITT; n=530)**

	<b>Ramucirumab + docetaxel (n=263)</b>	<b>Placebo + docetaxel (n=267)</b>
Platinum-based therapy	257 (98)	261 (98)
Cisplatin	159 (60)	182 (68)
Carboplatin	95 (36)	78 (29)
Oxaliplatin	1 (<1)	0
Platinum, not otherwise specified	2 (<1)	1 (<1)
Non-platinum-based therapy	257 (98)	261 (98)
Gemcitabine	231 (88)	236 (88)
Methotrexate/Vinblastine/Doxorubicin	16 (6)	16 (6)
Other	2 (<1)	5 (2)
Epirubicin/Methotrexate/Mitomycin	1 (<1)	0
Epirubicin/Methotrexate	0	1 (<1)
Methotrexate/Vinblastine	1 (<1)	1 (<1)
Etoposide	0	1 (<1)
Methotrexate sodium/Vinblastine	0	1 (<1)
Paclitaxel	1 (<1)	1 (<1)
None	7 (3)	4 (1)
Immune checkpoint inhibitor therapy	19 (7)	26 (10)
Atezolizumab	10 (4)	10 (4)
Pembrolizumab	5 (2)	9 (3)
Durvalumab	1 (<1)	2 (<1)
Nivolumab	0	2 (<1)
Pembrolizumab or placebo	0	1 (<1)
Nivolumab or placebo	1 (<1)	0
Anti-PD-L1, not otherwise specified	1 (<1)	1 (<1)
Bgba317 (anti-PD-1)	1 (<1)	1 (<1)
Antiangiogenic therapy	0	1 (<1)
Ramucirumab	0	1 (<1)
All Other	1 (<1)	3 (1)
Emactuzumab	1 (<1)	0
Denosumab	0	1 (<1)
Ayurvedic Preparation, not otherwise specified	0	1 (<1)
Cancer peptide vaccine	0	1 (<1)

Abbreviation: ITT = intent-to-treat.

<sup>†</sup>Patients may have received more than one type of therapy.

**Table S3: Exposure (safety population, n=523)**

	<b>Ramucirumab + docetaxel (n=258)</b>	<b>Placebo + docetaxel (n=265)</b>
<b>Ramucirumab or placebo</b>		
Number of patients	258	265
Median duration of therapy (IQR), weeks	12·1 (6-21)	9·9 (6-21)
Median number of cycles (IQR)	4 (2-7)	3 (2-6)
No. of patients completing at least 2 cycles, (%)	226 (88)	236 (89)
No. of patients completing at least 4 cycles, (%)	136 (53)	127 (48)
No. of patients completing at least 6 cycles, (%)	95 (37)	87 (33)
No. of patients completing at least 8 cycles, (%)	56 (22)	51 (19)
Median relative dose intensity (IQR)	99·6 (94·5-100·1)	99·6 (95·5-100·1)
<b>Docetaxel</b>		
Number of patients	258	265
Median duration of therapy (IQR), weeks	12·1 (6-18)	9·9 (6-18)
Median number of cycles (IQR)	4 (2-6)	3 (2-6)
No. of patients completing at least 2 cycles, (%)	228 (88)	233 (88)
No. of patients completing at least 4 cycles, (%)	137 (53)	128 (48)
No. of patients completing at least 6 cycles, (%)	93 (36)	84 (32)
No. of patients completing at least 8 cycles, (%)	19 (7)	17 (6)
Median relative dose intensity (IQR)	98·3 (90·9-100·1)	98·8 (92·9-100·1)

Abbreviation: IQR = interquartile range; No. = Number



**Table S4: Investigator-assessed efficacy endpoints, first 437 randomised patients**

	<b>Ramucirumab + docetaxel (n=216)</b>	<b>Placebo + docetaxel (n=221)</b>	
<b>Progression-free survival</b>			<b>P Value</b>
Deaths or disease progressions, no. (%)	158 (73)	183 (83)	
Median, months (95% CI)	4.07 (2.96 to 4.47)	2.76 (2.60 to 2.96)	
Hazard ratio (95% CI)	0.757 (0.607 to 0.943)		0.0118
3-month PFS rate, % (95% CI)	57.1 (49.9 to 63.7)	42.3 (35.5 to 49.0)	0.0028
6-month PFS rate, % (95% CI)	28.5 (22.0 to 35.3)	18.9 (13.7 to 24.7)	0.0309
9-month PFS rate, % (95% CI)	16.5 (11.0 to 22.9)	10.0 (6.1 to 14.9)	0.0862
12-month PFS rate, % (95% CI)	11.9 (7.1 to 18.0)	4.5 (1.5 to 10.1)	0.0374
<b>Best overall response, No. (%)</b>			
Complete response	9 (4.2)	3 (1.4)	
Partial response	44 (20.4)	28 (12.7)	
Stable disease	84 (38.9)	93 (42.1)	
Progressive disease	49 (22.7)	73 (33.0)	
Not evaluable	30 (13.9)	24 (10.9)	
Objective response rate, % (95%CI)	24.5 (18.8 to 30.3)	14.0 (9.4 to 18.6)	N/A
Disease control rate, % (95%CI)	63.4 (57.0 to 69.8)	56.1 (49.6 to 62.7)	N/A

Abbreviations: CI = confidence interval; N/A = not applicable due to gatekeeping trial design; no. = number; PFS = progression-free survival

Data are n (%) unless otherwise indicated.

**Table S5: Adverse events leading to death, regardless of causality**

	<b>Ramucirumab + docetaxel (n=258)</b>	<b>Placebo + docetaxel (n=265)</b>
Any	15 (6)	11 (4)
Sepsis	4 (2)	0
Death <sup>†</sup>	1 (<1)	2 (<1)
Renal failure	2 (<1)	0
Pneumonia	0	2 (<1)
Pneumonitis	1 (<1)	1 (<1)
Basilar artery thrombosis	1 (<1)	0
Cardiac arrest	1 (<1)	0
Enterovesical fistula	1 (<1)	0
Gastric haemorrhage	1 (<1)	0
Neutropenic sepsis	1 (<1)	0
Pneumonia aspiration	1 (<1)	0
Respiratory tract infection	1 (<1)	0
Asthenia	0	1 (<1)
Lung infection	0	1 (<1)
Pulmonary embolism	0	1 (<1)
Pulmonary hypertension	0	1 (<1)
Sudden death	0	1 (<1)
Toxic shock syndrome	0	1 (<1)

<sup>†</sup>No further information was available.

## References

1. Sternberg CN, Yagoda A, Scher HI, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989; **64**(12): 2448-58.
2. Loehrer PJ, Sr., Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992; **10**(7): 1066-73.
3. Saxman SB, Propert KJ, Einhorn LH, et al. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1997; **15**(7): 2564-9.
4. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000; **18**(17): 3068-77.
5. Raggi D, Miceli R, Sonpavde G, et al. Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. *Ann Oncol* 2016; **27**(1): 49-61.
6. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med* 2017; **376**(11): 1015-26.
7. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016; **387**(10031): 1909-20.
8. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017; **18**(3): 312-22.
9. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an Anti-Programmed Death-Ligand 1 Antibody, In Patients With Refractory Metastatic Urothelial Carcinoma: Results From a Multicenter, Phase Ib Study. *J Clin Oncol* 2017; **35**(19): 2117-24.
10. Hahn NM. Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma (UC). *J Clin Oncol* 2017; **35** (suppl; abstr 4525).
11. Dickinson AJ, Fox SB, Persad RA, Hollyer J, Sibley GN, Harris AL. Quantification of angiogenesis as an independent predictor of prognosis in invasive bladder carcinomas. *Br J Urol* 1994; **74**(6): 762-6.
12. Necchi A, Mariani L, Zaffaroni N, et al. Pazopanib in advanced and platinum-resistant urothelial cancer: an open-label, single group, phase 2 trial. *The lancet oncology* 2012; **13**(8): 810-6.
13. Petrylak DP, Tagawa ST, Kohli M, et al. Docetaxel As Monotherapy or Combined With Ramucirumab or Icrucumab in Second-Line Treatment for Locally Advanced or Metastatic Urothelial Carcinoma: An Open-Label, Three-Arm, Randomized Controlled Phase II Trial. *J Clin Oncol* 2016; **34**(13): 1500-9.
14. Jaeger TM, Weidner N, Chew K, et al. Tumor angiogenesis correlates with lymph node metastases in invasive bladder cancer. *J Urol* 1995; **154**(1): 69-71.
15. Sato K, Sasaki R, Ogura Y, et al. Expression of vascular endothelial growth factor gene and its receptor (flt-1) gene in urinary bladder cancer. *Tohoku J Exp Med* 1998; **185**(3): 173-84.
16. Crew JP, O'Brien T, Bicknell R, Fuggle S, Cranston D, Harris AL. Urinary vascular endothelial growth factor and its correlation with bladder cancer recurrence rates. *J Urol* 1999; **161**(3): 799-804.

17. Inoue K, Slaton JW, Karashima T, et al. The prognostic value of angiogenesis factor expression for predicting recurrence and metastasis of bladder cancer after neoadjuvant chemotherapy and radical cystectomy. *Clin Cancer Res* 2000; **6**(12): 4866-73.
18. Xia G, Kumar SR, Hawes D, et al. Expression and significance of vascular endothelial growth factor receptor 2 in bladder cancer. *J Urol* 2006; **175**(4): 1245-52.
19. Balar AV, Apolo AB, Ostrovnaya I, et al. Phase II Study of Gemcitabine, Carboplatin, and Bevacizumab in Patients With Advanced Unresectable or Metastatic Urothelial Cancer. *Journal of Clinical Oncology* 2013; **31**(6): 724-30.
20. Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol* 2010; **28**(5): 780-7.
21. Bellmunt J, Orsola A, Leow J, Wiegel T, De Santis M, Horwich A. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology* 2014; **25**(suppl\_3): iii40-iii8.
22. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24**(19): 3187-205.
23. Devlin N, Shah K, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. 2016.
24. Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol* 2010; **28**(11): 1850-5.
25. Sonpavde G, Pond GR, Fougeray R, et al. Time from prior chemotherapy enhances prognostic risk grouping in the second-line setting of advanced urothelial carcinoma: a retrospective analysis of pooled, prospective phase 2 trials. *European urology* 2013; **63**(4): 717-23.
26. McCaffrey JA, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997; **15**(5): 1853-7.
27. Petrylak DP. Immunotherapy: The Wave of the Future in Bladder Cancer? *Clin Genitourin Cancer* 2017; **15**(3S): S3-S17.
28. Petrylak DP, Arkenau H-T, Perez-Gracia JL, et al. A multicohort phase I study of ramucirumab (R) plus pembrolizumab (P): Interim safety and clinical activity in patients with urothelial carcinoma. American Society of Clinical Oncology; 2017.
29. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *The lancet oncology* 2016; **17**(11): 1497-508.
30. Golan T, Lin C-C, Fu S, et al. PD-010A multi-cohort phase 1 study of ramucirumab plus durvalumab: Preliminary safety and clinical activity in patients with locally advanced and unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma. *Annals of Oncology* 2017; **28**(suppl\_3).
31. Herbst R, Martin-Liberal J, Calvo E, et al. 90PDP Previously treated advanced NSCLC cohort from a multi-disease phase 1 study of ramucirumab (R) plus pembrolizumab (P): Efficacy and safety data. *Annals of Oncology* 2017; **28**(suppl\_2).